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Efficacy of Tirofiban combined with oral antiplatelet therapy in progressive ischemic stroke: A systematic review and meta-analysis

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Abstract. This meta-analysis aimed to evaluate the safety and efficacy of combining tirofiban with oral antiplatelet agents in treating patients with progressive ischemic stroke. The investigators searched several databases, including PubMed, Web of Science, the Cochrane Library, CNKI, VIP, WanFang Data and Sinomed. The search was restricted to literature published before May 5, 2025, without any language restrictions. Stata software 17.0 was used to analyze the results and assess risk of bias. A total of 19 studies comprising 3,667 patients were included in the analysis. Furthermore, statistically significant differences (P<0.05) were observed when comparing the tirofiban group and the control group regarding the incidence of achieving a 3-month modified Rankin scale (mRS) score of 0-2, the National Institutes of Health Stroke Scale score, the mRS score, activities of daily living, the platelet aggregation rate, the platelet adhesion rate and the effective rate. However, no significant differences (P>0.05) were detected in the risks of intracranial hemorrhage, other systemic hemorrhage, mortality rate and serious adverse events between the two groups. The study was conducted according to the preferred reporting items for systematic reviews and meta-analyses guidelines and registered with PROSPERO (no. CRD42025633357), and the findings suggested that tirofiban-augmented antiplatelet regimens safely improve clinical outcomes in progressive cerebral infarction, particularly when combined with dual oral antiplatelet agents.

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Abbreviations: PIS, progressive ischemic stroke; PIC, progressive cerebral infarction; END, early neurological deterioration; AIS, acute ischemic stroke; RCT, randomized controlled trial; OR, odds ratio; SMD, standardized mean difference; NIHSS, the National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; ADL, activities of daily living; BI, Barthel index; PAgR, platelet aggregation rate; PAdR, platelet adhesion rate; sICH, symptomatic intracerebral hemorrhage; ICH, intracranial hemorrhage; CNKI, China National Knowledge Infrastructure; VIP, China Science and Technology Journal Database

Key words: antiplatelet drugs, aspirin, clopidogrel, progressive ischemic stroke, tirofiban, meta-analysis

Introduction

Ischemic stroke, accounting for roughly 87% of all strokes, is the most prevalent type of cerebrovascular accident. It primarily results from a disruption in cerebral blood flow (1). Among them, progressive cerebral infarction (PCI) constitutes between 26 and 43% (2) of all cerebral infarction cases and is associated with elevated mortality and disability rates. The pathogenesis of PCI is complex (3-6), involving thrombus expansion and regeneration, reduced cerebral perfusion, cerebral edema and failure to promptly establish collateral circulation within the ischemic region (7), thereby resulting in cerebral tissue hypoxia and subsequently presenting symptoms of neurological dysfunction. Currently, there is no accepted definition of progressive ischemic stroke (PIS). In both domestic and international studies and reports, the relevant concepts predominantly comprise early neurological deterioration, progressive neurological deficits, stroke progression and early recurrent ischemic stroke. The difference lies in the time window and the assessment method, and there is a significant variation in treatment options. Currently, treatment mainly includes specific and fundamental approaches. As discussed in this article, the combination of tirofiban with oral antiplatelet drugs is a specific treatment.

Glycoprotein IIb/IIIa, a key receptor found on the surface of platelets, plays an essential role in regulating platelet aggregation. Glycoprotein IIb/IIIa inhibitors, a category of highly selective platelet antagonists, bind specifically to the glycoprotein IIb/IIIa receptors on platelet surfaces. These inhibitors effectively and reversibly impede fibrin attachment to the aforementioned receptors through this binding interaction, thus preventing platelet aggregation (8). Experimental data from stroke animals treated with glycoprotein IIb/IIIa inhibitors indicated that, even when administered later, the volume of the infarct may still be reduced (9).

Tirofiban is a reversible non-peptide platelet GP IIb/IIIa receptor antagonist. It directly inhibits the GP IIb/IIIa receptor, blocking fibrinogen crosslinking (10). Tirofiban acts rapidly, with immediate effect upon intravenous administration, making it suitable for rapid anti-thrombotic action in acute situations. Conversely, aspirin and clopidogrel are primarily used for long-term prevention. Therefore, Tirofiban provides a rapid, controllable and reversible antiplatelet effect in acute thrombotic events through its unique GP IIb/IIIa targeting mechanism, complementing the role of aspirin and clopidogrel.

Meanwhile, Tirofiban is highly selective and can reversibly prevent platelet aggregation. Among them, tirofiban reduces the probability of thrombotic events during percutaneous coronary intervention (11). Certain studies have demonstrated that tirofiban can enhance neurological function 90 days after acute ischemic stroke (12). Additionally, it has been indicated that intravenous tirofiban markedly improved the clinical outcomes of patients with PIS (13). However, it has also been associated with a higher occurrence of fatal intracranial hemorrhage (ICH) (14). Therefore, it is essential to study both the therapeutic effect of tirofiban in patients with progressive stroke and its associated safety profile.

The medical literature persists with controversy regarding the impact of tirofiban on progressive stroke. The extant evidence is predominantly derived from observational, non-randomized or retrospective studies, with a paucity of randomized controlled trials (RCTs). Therefore, a systematic review of the included RCTs and retrospective and cohort studies was conducted to assess their safety and efficacy, providing reliable evidence.

Patients and methods

Registration. This meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (15). It has been registered at PROSPERO (https://www.crd.york.ac.uk/PROSPERO/) under the ID no. CRD42025633357.

Search strategy. The relevant literature was searched using the following databases: PubMed (https://pubmed.ncbi.nlm.nih.gov/), Cochrane Library (https://www.cochranelibrary.com/), Web of Science (https://www.webofscience.com/), China National Knowledge Infrastructure (CNKI; https://www.cnki.net/), WanFang Data (https://www.wanfangdata.com.cn/), China Science and Technology Journal Database (VIP; http://www.cqvip.com/) and Sinomed (http://www.sinomed.ac.cn/). The objective was to identify RCTs and cohort studies, comparing tirofiban combined with oral antiplatelet drugs to oral antiplatelet drugs alone in treating patients with PIS. The comprehensive search strategy relied on the following search terms: ('PIS', 'progressive cerebral infarction' or 'progressive stroke' or 'progressive cerebral thrombosis' or 'early neurological deterioration') and ('tirofiban'). Furthermore, the reference lists of eligible studies and related reviews were manually screened to identify other potentially relevant literature for inclusion. The search was conducted on May 5th, 2025, covering literature published up to May 5th, 2025 without any language restrictions, and strictly followed the PRISMA 2020 guidelines. The PRISMA flowchart (Fig. 1) details the study selection process.

Inclusion and exclusion criteria. The study's inclusion criteria were defined as follows: First, the study type was confined to prospective or retrospective cohort studies and RCTs. Observational studies were included despite their inherent risk of bias (e.g., selection bias, unmeasured confounding). The Newcastle-Ottawa Scale (NOS) was used to assess their quality, although residual bias might persist (16). These studies were designed to explore the application of tirofiban in combination with oral antiplatelet drugs in treating patients diagnosed with PIS, irrespective of whether blinding procedures were incorporated. Secondly, PIS is defined as an increase of ≥2 points from baseline in the National Institutes of Health Stroke Scale (NIHSS) score (17) within 72 h of stroke onset. The included studies used different definitions, but all met the core criterion of neurological deterioration within 72 h. The subjects of this study were carefully selected. The subjects were patients with PIS who had a persistent decline in neurological function after onset, an NIHSS score of no less than 2 and an onset time within 72 h. Thirdly, concerning the intervention measures, the control group was subjected to conventional treatment along with oral antiplatelet drug therapy. By contrast, the experimental group was further administered tirofiban in addition to the control group's treatment protocol. Lastly, the outcome measures were bifurcated into efficacy and safety measures. The efficacy measures encompassed the NIHSS score, modified Rankin scale (mRS) score (18), activities of daily living (ADL) scores (19), Barthel index (BI) scale scores (19), platelet aggregation rate (PAgR) and platelet adhesion rate (PAdR) (20,21). The safety measures comprised the incidence of intracranial hemorrhage, hemorrhage in other systems, mortality rate and serious adverse events. The exclusion criteria were single-arm trials, animal studies, conference abstracts, case reports and any reports from which data cannot be extracted based on published articles. Also excluded were studies focusing on non-PIS during the entire surgical process, those where the intervention did not involve the combination of tirofiban with oral antiplatelet drugs and studies in which each group had fewer than 25 participants.

Data extraction. A total of two authors (YY and YFJ) conducted the literature screening independently and then cross-verified the results. In the event of any disagreement, they consulted a third researcher until a consensus was ultimately reached. The data retrieved from the literature comprised the first author's name, publication year, study type, sample size, therapeutic outcome and safety outcome. The efficacy outcomes were as follows: i) 3-month mRS score of 0-2,

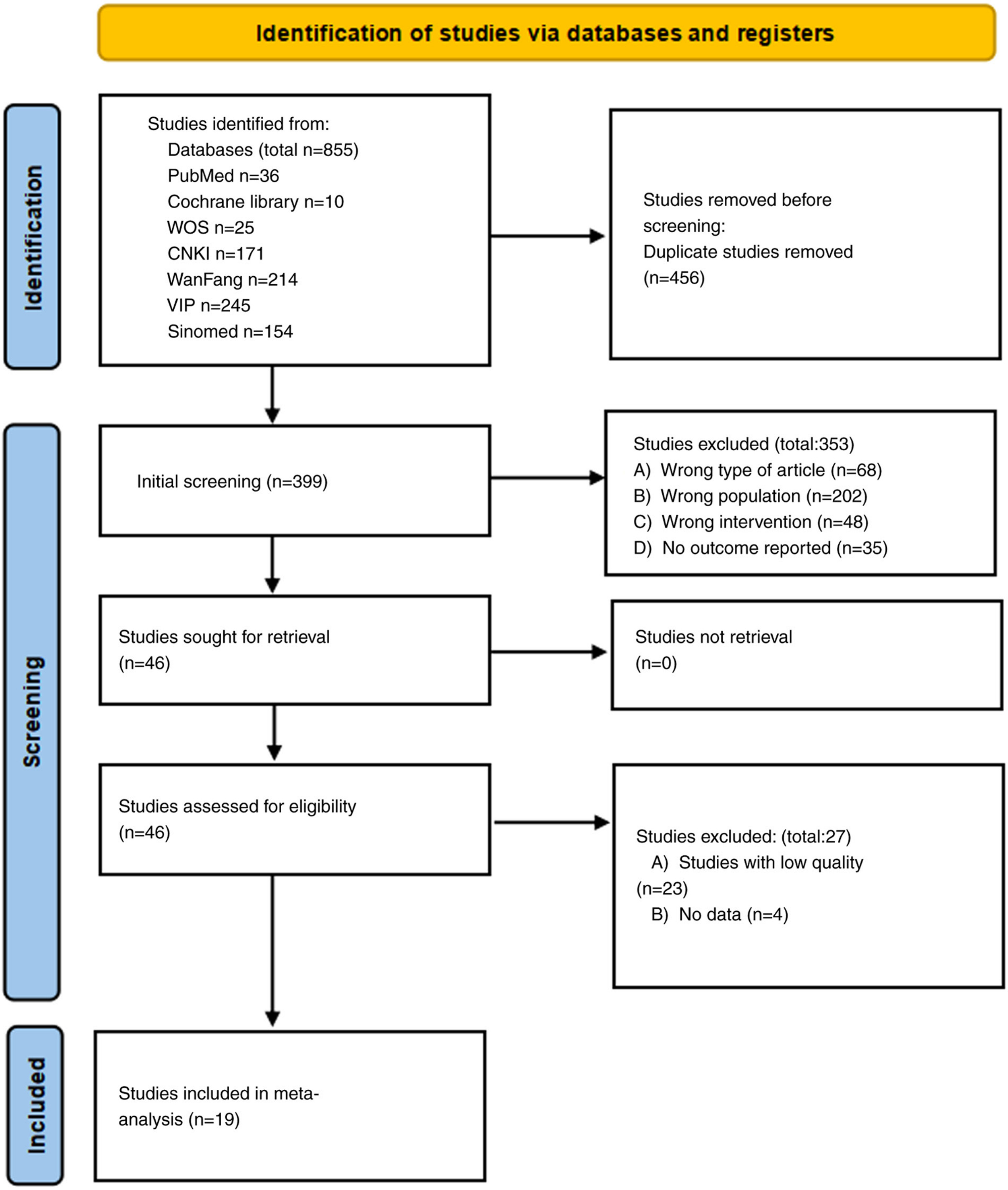

Figure 1. Flow diagram of the study selection. WOS, Web of Science; CNKI, China National Knowledge Infrastructure.

ii) NIHSS score, iii) ADL score, iv) PAgR, v) PAdR and vi) effective rate. The following safety outcomes were evaluated: i) Symptomatic ICH (sICH), ii) other systemic hemorrhage, iii) mortality rate and iv) serious adverse events.

Quality assessment. The quality of RCTs was appraised using the Cochrane Risk of Bias Tool (22). For observational studies, quality was assessed using the NOS, which assesses three domains: Participant selection (0 to 4 points), inter-group comparability (0 to 2 points) and outcome assessment (0 to 3 points), with a maximum score of 9. It is important to note that no NOS score threshold was pre-set as an inclusion criterion; all observational studies that met the initial inclusion criteria (e.g., study design, population, interventions) were included in the meta-analysis, regardless of their potential NOS score. After assessing quality, it was found that the six included observational studies all had NOS scores between 7 and 9.

Statistical analysis. The data analysis was conducted with Stata software (version 17.0; StataCorp. LP). The random-effects model was employed for categorical variables to calculate the pooled estimates of odds ratios (ORs), while the mean differences were computed for continuous variables. Heterogeneity was evaluated via the Cochran Q test and the I^2 test. When I^2 was <50% or P>0.1 (indicating low heterogeneity), the fixed-effects model was utilized. Continuous data were evaluated using the standardized mean difference (SMD) and its 95% CI, whereas binary data were analyzed with the OR and 95% confidence interval. P<0.05 was regarded as statistically significant. Publication bias was evaluated by visually examining the data and calculating the P-value with Egger's test and Begg's test. If publication risk of bias was detected, the nonparametric trim-and-fill method was further used to adjust for the potential effect of missing studies. Additionally, subgroup analyses were performed to explore the potential sources of heterogeneity across studies. Based on clinical relevance, subgroup analyses were pre-defined according to the antiplatelet treatment regimens (monotherapy and dual therapy), but comparisons between subgroups should be considered exploratory analyses. To explore the potential source of heterogeneity, subgroup analyses were further performed based on the duration of tirofiban administration (short course vs. long course). A short course was defined as tirofiban infusion ≤48 h and a long course as >48 h, according to the median duration reported in included studies.

Sensitivity analyses. To further validate the robustness of the primary study results and to account for possible biases in the mixed study design, sensitivity analyses were performed for only 13 RCTs. The statistical methods were consistent with the main analysis (using Stata 17.0 software; ORs were used for categorical outcomes and SMDs for continuous outcomes).

Results

Literature search results. A total of 855 relevant entries were identified through database searches. After eliminating 456 redundant articles, excluding 353 studies upon reading the titles, abstracts and perusing the full texts, 46 full texts remained for detailed evaluation. Among these, 27 articles were further excluded (23 due to low quality and 4 due to unavailable data). Eventually, 19 articles were included (10,23-40), of which 12 were published in Chinese and 7 in English. Fig. 1 illustrates the detailed screening process.

Characteristics of included studies. A total of 19 studies were included in the meta-analysis. All articles were published between 2020 and 2024. A total of 3,667 patients were included, among which 1,859 were in the experimental group and 1,808 were in the control group. Table I presents the key characteristics of the individual studies included in the analysis.

Quality assessment. Two authors (YY and YFJ) assessed the quality of 13 RCTs using the Cochrane risk of bias tool. All studies were randomised, with one study not describing a specific method of randomisation and 12 studies having specified it. All RCTs were at low risk of attrition bias. In addition, none of the 13 studies selectively reported their findings and only four studies had incomplete outcome measures. Regarding blinding bias of participants and investigators, 12 of the 13 RCTs had high or unclear risk for blinding and five studies were inadequately allocated for concealment (selection bias). Risk of bias maps were generated using Review Manager 5.3 (https://tech.cochrane.org/revman) and the specific results are shown in Fig. 2. The NOS scale was used to assess six observational studies (see Table SI for full assessment details). No study was excluded based on the NOS score; all six studies met the initial inclusion criteria (e.g., focusing on PIS and comparing ticagrelor combined with oral antiplatelet agents vs. oral antiplatelet agents alone) and were included in the analysis. Their NOS scores ranged from 7 to 8 (with a median of 8), demonstrating high scores in selection (all ≥3/4) and comparability (all ≥1/2), indicating a low risk of bias.

Efficacy outcomes

mRS score (0-2 within 3 months). A total of 4 studies (10,23,24,37) reporting on the occurrence of mRS scores ranging from 0 to 2 within 3 months were comprehensively analyzed. Data were obtained from 2,032 patients, among whom 1,028 cases received tirofiban in combination with oral antiplatelet drugs, while 1,004 cases were treated only with oral antiplatelet drugs. Heterogeneity analysis showed I^2=0% and P>0.1 (low heterogeneity), so the fixed-effects model was used. The pooled OR showed the experimental group had a higher 3-month mRS 0-2 rate [OR=1.31, 95% CI (1.10, 1.58), P=0.003] (Fig. 3A).

NHISS score. A total of 19 studies comparing the NHISS scores after treatment between the two groups were comprehensively analyzed. Among these, the data of 3 studies (23,29,39) did not follow a normal distribution and the specific arithmetic means and standard deviations were not provided explicitly in 4 studies (10,24,26,36). For the remaining 12 studies (25,27,28,30-35,37,38,40), 1,341 patients were included, with 672 placed in the experimental group and 669 in the control group. I^2=80% and P<0.1 (high heterogeneity), so the random-effects model was used. The result demonstrated that the experimental group had a significantly lower NHISS score compared to the control group [SMD=-1.22, 95% CI (-1.49, -0.95), P<0.01]. Subgroup analysis was subsequently conducted based on different intervention measures, using tirofiban combined with oral single antiplatelet drugs or oral dual antiplatelet drugs. In the oral single antiplatelet drug subgroup, three studies involving 249 patients were incorporated, with 121 in the experimental group and 128 in the control group (28,31,37). Overall, the NHISS score of the experimental group was significantly lower than that of the control group [SMD=-0.99, 95% CI (-1.67, -0.31), P=0.004]. A total of nine studies, comprising 1,092 patients, were included in the oral dual antiplatelet drug subgroup (25,27,30,32-35,38,40). The experimental group comprised 551 participants, while the control group included 541 individuals. The analysis revealed that the NHISS score for the experimental group was significantly lower than that for the control group [SMD=-1.29, 95% CI (-1.58, -1.00), P<0.01]. The difference in the NHISS score between the experimental and control groups was more noticeable in the tirofiban combined with oral dual antiplatelet drug subgroup than in the subgroup using oral single antiplatelet drugs (Fig. 3B).

At the same time, an additional subgroup analysis included 12 studies for which data were available. In seven studies (n=859) in the short-course subgroup (27,28,32,33,37,38,40),

Table I. Baseline characteristics of the included studies.

Author/s, year	Year	Design	Sample	T	C	Safety outcome	Efficacy outcome	Measures	Maintenance of 0.1 μg/(kg min)	Treatment course	(Refs.)
Zi *et al*, 2023	2023	RCT	1177	606	571	①③④	90mRS (0-2)	1	for 48 h	SC	(10)
Han *et al*, 2022	2022	RCT	357	177	180	①②③	90mRS (0-2)	1	for 48 h	SC	(23)
Zhao *et al*, 2024	2024	RCT	384	196	188	①③④	90mRS (0-2)	1	for 71.5 h	LC	(24)
Chen *et al*, 2024	2024	RCT	70	35	35	②④	Evaluation of therapeutic efficacy, NIHSS, ADL	2	for 72 h	LC	(25)
Sun *et al*, 2022	2022	RCT	127	68	59	NA	PAdR, PAgR	1	for 24 h	SC	(26)
Liu *et al*, 2024	2024	RCT	80	40	40	②④	Evaluation of therapeutic efficacy, NHISS	2	for 48 h	SC	(27)
Li *et al*, 2024	2024	RCT	108	54	54	②④	mRS, NHISS, ADL	1	for 48 h	SC	(28)
Li *et al*, 2024	2024	RCT	80	40	40	②	Evaluation of therapeutic efficacy	2	for 48 h	SC	(29)
Luo *et al*, 2020	2020	RCT	90	45	45	NA	NHISS, BI, PAdR, PAgR	2	for 2 w	LC	(30)
Xiao *et al*, 2024	2024	RCT	66	33	33	②④	Evaluation of therapeutic efficacy, NHISS, ADL, PAdR, PAgR	1	for 2 w	LC	(31)
Duan *et al*, 2024	2024	RCT	120	60	60	①②	Evaluation of therapeutic efficacy, NHISS, BI, PAdR, PAgR	2	for 48 h	SC	(32)
Bian *et al*, 2024	2024	RCT	317	167	150	①②	NHISS, BI, PAdR, PAgR	2	for 48 h	SC	(33)
Liao *et al*, 2020	2020	RCT	106	53	53	①②	Evaluation of therapeutic efficacy, mRS, NHISS, PAdR, PAgR	2	for 108 h	LC	(34)
Du *et al*, 2022	2022	CS	150	75	75	①②	Evaluation of therapeutic efficacy, mRS, NHISS, BI, PAdR, PAgR	2	for 72 h	LC	(35)
Wang *et al*, 2020	2020	CS	108	54	54	①②③	mRS	2	for 24 h	SC	(36)
Zhang *et al*, 2023	2023	RS	75	34	41	①	90mRS (0-2), NHISS	1	for 48 h	SC	(37)
Zhang *et al*, 2021	2021	CS	104	52	52	①②③	Evaluation of therapeutic efficacy, mRS, NHISS	2	for 24 h	SC	(38)
Ma *et al*, 2020	2020	CS	93	46	47	①②	mRS	2	for 24 h	SC	(39)
Jiang *et al*, 2020	2020	CS	55	24	31	①②	mRS, NHISS	2	for 24 h	SC	(40)

T, tirofiban group; C, control group; RCT, randomized controlled trial; CS, cohort study; RS, retrospective study; ①, sICH; ②, any ICH; ③, 3-month mortality; ④, serious adverse event (except for any sICH); ADL, activity of daily living scale; NHISS, National Institutes of Health Stroke Scale (after treatment); 90mRS, 90-day modified Rankin scale; BI, Barthel index; NA, not available; PAdR, platelet adhesion rate; PAgR, platelet aggregation rate; 1, Tirofiban combined with a single oral antiplatelet drug (aspirin or clopidogrel); 2, Tirofiban combined with dual antiplatelet drugs (aspirin and clopidogrel); LC, long course of treatment; SC, short course of treatment; w, weeks.

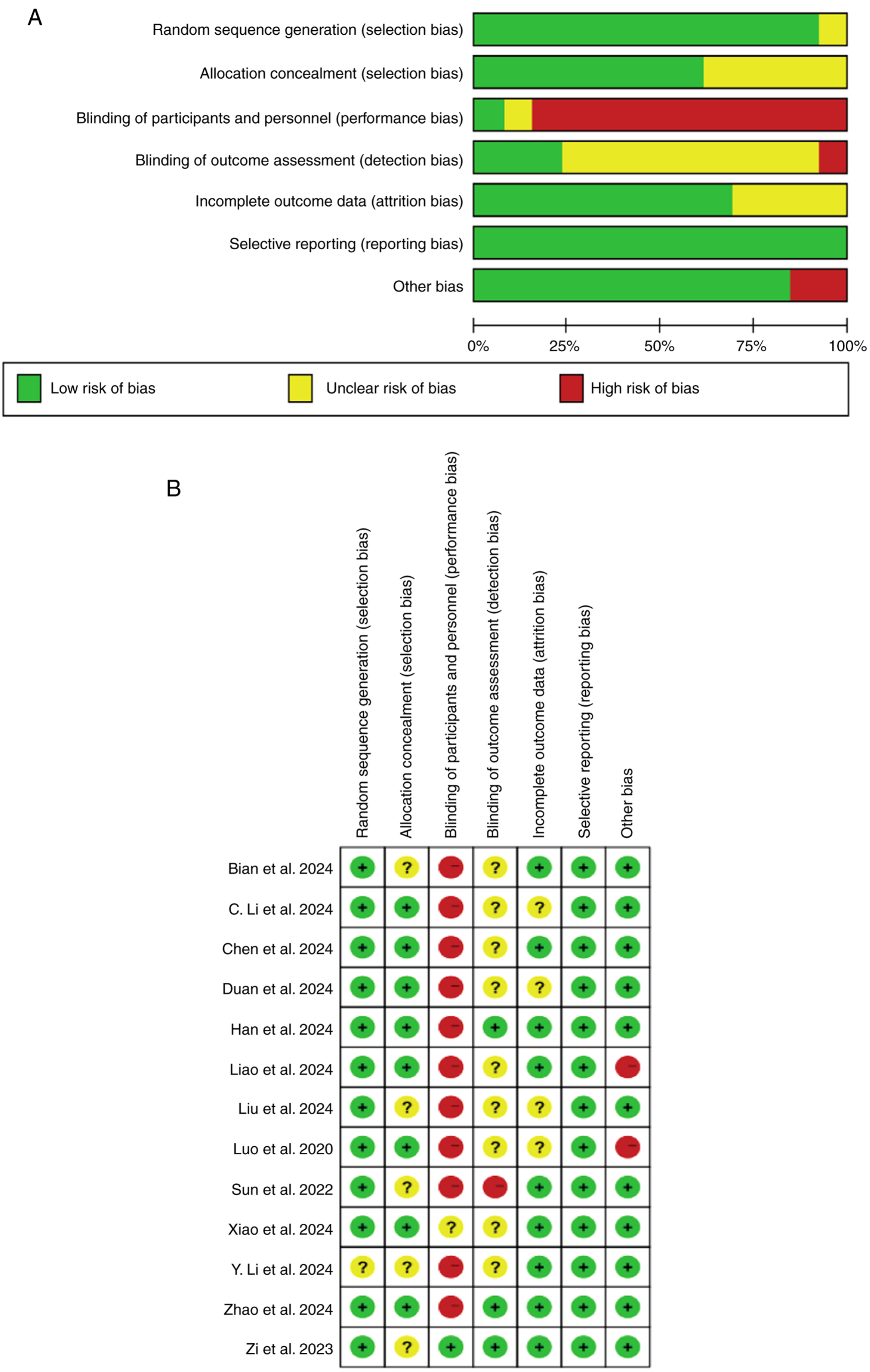

Figure 2. Bias risk diagram of 13 randomized controlled trials analyzed by Cochrane. (A) Risk of bias summary and (B) risk of bias graph.

NIHSS scores were significantly lower in the experimental group compared with the control group [SMD=-1.15, 95% CI (-1.51, -0.79), P<0.001]. The heterogeneity in this subgroup was high (I^2=81.3%, P<0.001). In five studies (n=482) in the

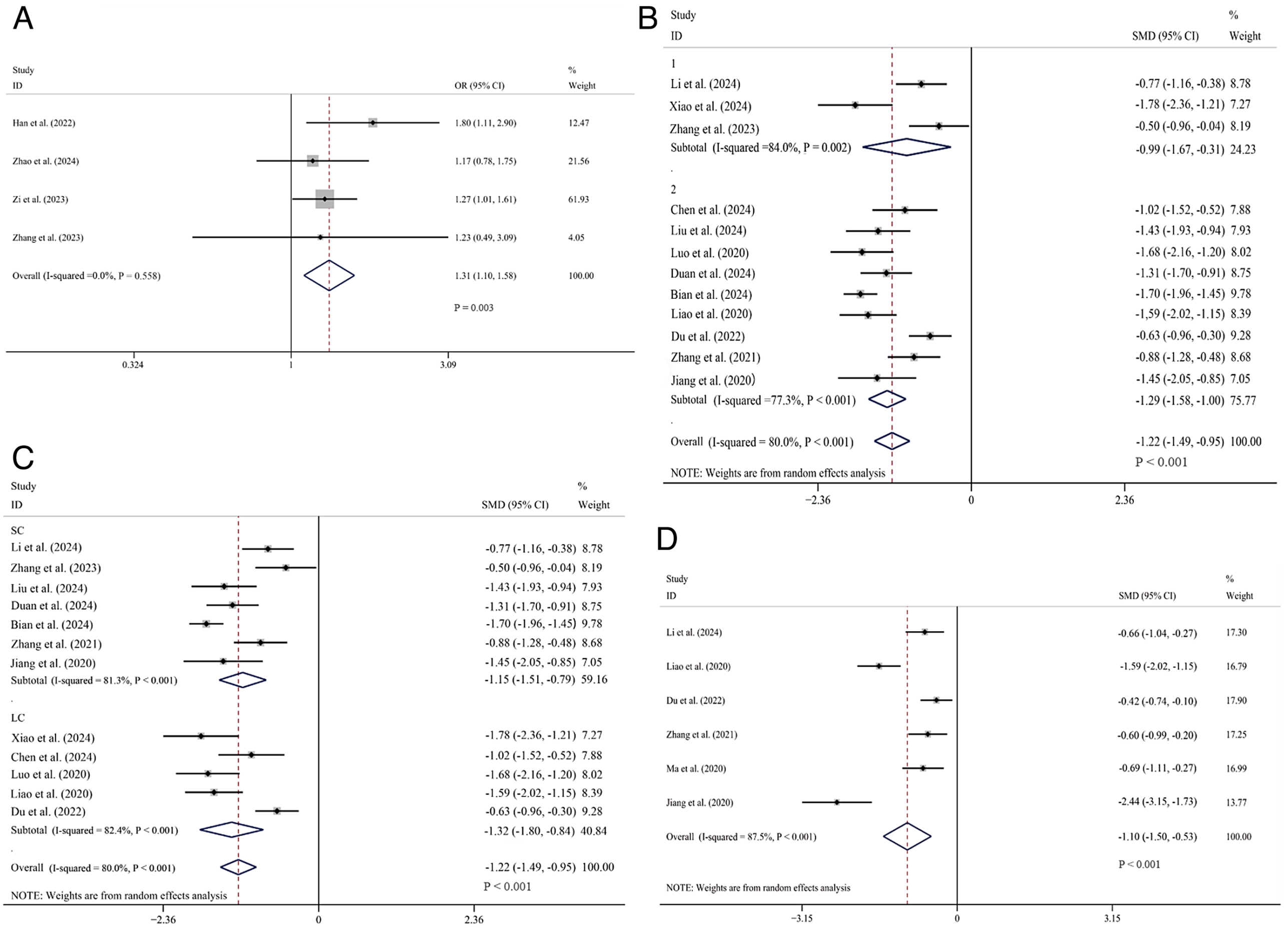

Figure 3. Forest plots comparing tirofiban vs. non-tirofiban therapy. (A) Proportion of patients with mRS scores 0-2 at 3 months. (B) Subgroup analysis of NIHSS scores. (C) NIHSS score subgroup analysis stratified by tirofiban treatment duration. (D) mRS scores. mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; ADL, Activities of Daily Living; 1, oral single antiplatelet drug; 2, oral dual antiplatelet drugs; LC, long course of treatment; SC, short course of treatment; SMD, standard mean deviation; CI, confidence intervals; OR, odds ratio.

long-duration subgroup (25,30,31,34,35), NIHSS scores were also significantly lower in the trial group [SMD=-1.32, 95% CI (-1.80, -0.84), P<0.001], with similarly high heterogeneity (I^2=82.4%, P<0.001). The overall effect remained significant [SMD=-1.22, 95% CI (-1.49, -0.95), P<0.001] under the random-effects model, with considerable heterogeneity observed across all studies (I^2=80.0%, P<0.001). This suggests that tirofiban improved neurological function regardless of the duration of treatment, but there was no reduction in heterogeneity in either subgroup (Fig. 3C).

mRS score. A total of 6 studies (28,34,35,38-40) comparing the mRS scores after treatment were comprehensively analyzed. Data were retrieved from these studies, which involved 616 patients. Among them, 304 cases were included in the experimental group and 312 cases in the control group. Heterogeneity was significant (I^2=87.5%, P<0.1), and a random-effects model was used. Overall, it was demonstrated that the mRS score of the experimental group was markedly lower than that of the control group [SMD=-1.10, 95% CI (-1.50, -0.53), P<0.01] (Fig. 3D). Notably, a higher mRS score indicates more severe symptoms.

ADL score. A total of 3 studies (25,28,31) comparing ADL scores were comprehensively analyzed. Data were obtainable from these studies. There were 244 patients in total, with 122 in the experimental group and 122 in the control group. The heterogeneity was significant (I^2=78.9%, P<0.1) and a random-effects model was employed. Overall, the experimental group was shown to be superior to the control group in ADL scores [SMD=1.19, 95% CI (0.58, 1.80), P<0.01] (Fig. 4A).

BI index. A total of 3 studies (30,33,35) that reported on the BI index were included. The data retrievable from these studies involved a total of 557 patients, with 287 in the experimental group and 270 in the control group. A random-effects model was used due to significant heterogeneity (I^2=78.9%, P<0.1). Overall, the SMD was significantly >0, which indicated that the BI index of the experimental group was superior to that of the control group [SMD=1.36, 95% Cl (0.92, 1.79), P<0.01] (Fig. 4B).

PAgR. A total of 7 studies (26,30-35) involving the measurement of PAgR were comprehensively analyzed. Data can be obtained from these studies, with 976 patients in total, 501 in the experimental groups and 475 in the control groups. Significant heterogeneity was observed (I^2=92.4%, P<0.001) and a random-effects model was applied. It shows that the PAgR in the experimental group was significantly lower compared with that in the control group [SMD=-1.19, 95% CI (-1.71, -0.67), P<0.01]. Further subgroup analysis was

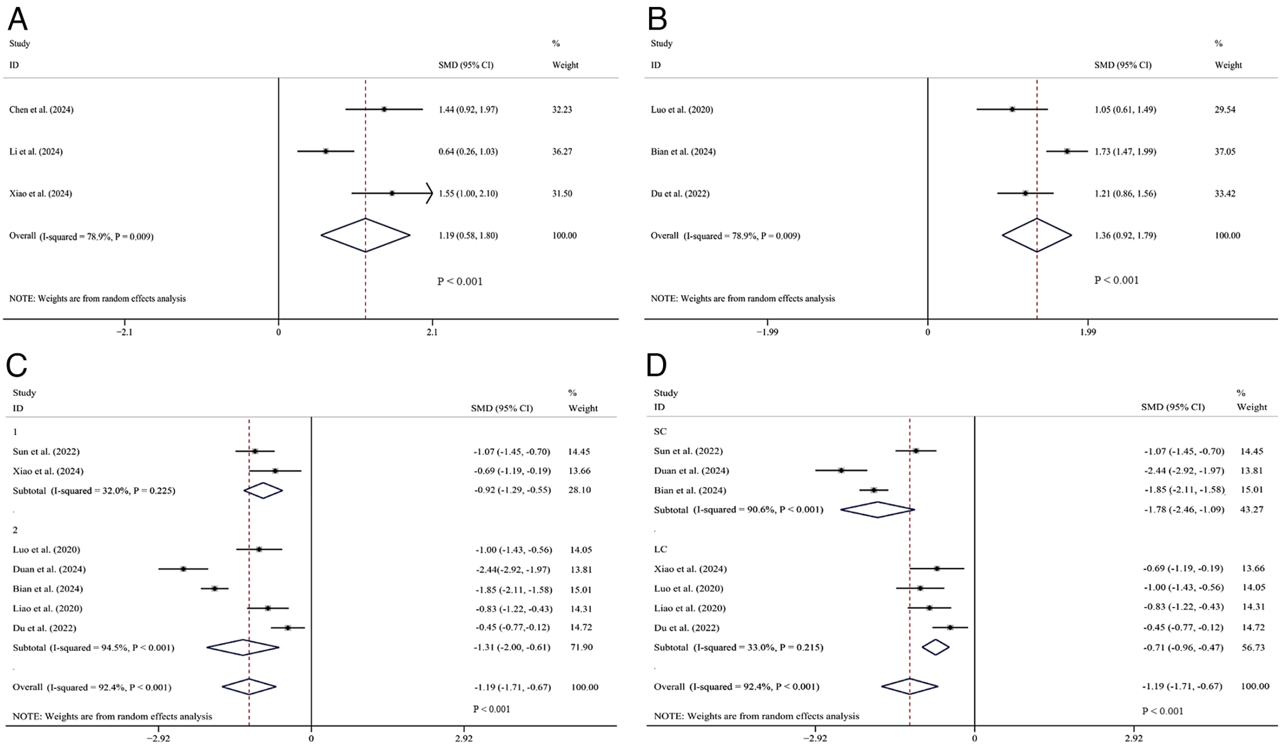

Figure 4. Forest plots comparing tirofiban therapy vs. non-tirofiban therapy for (A) ADL score, (B) BI score, (C) subgroup analysis of PAgR, and (D) subgroup analysis of PAgR based on tirofiban treatment duration. ADL, Activities of Daily Living; BI, Barthel Index; PAgR, platelet aggregation rate; 1, oral single antiplatelet drug; 2, oral dual antiplatelet drugs; LC, long course of treatment; SC, short course of treatment; SMD, standard mean deviation; CI, confidence intervals.

based on different intervention measures. In the single antiplatelet drug subgroup, two studies included 193 patients (101 in experimental group and 92 in control group) (26,31), and the PAgR of the experimental group was lower [SMD=-0.92, 95% CI (-1.29, -0.55), P<0.01]. In the oral dual antiplatelet drug subgroup, 5 studies included 783 patients (400 in experimental group and 383 in control group) (30,32-35), and the PAgR of the experimental group was lower [SMD=-1.31, 95% CI (-2.00, -0.61), P<0.01]. Obviously, in terms of the PAgR results, the experimental group had a more significant decrease in PAgR than the control group in the subgroup using a combination of tirofiban and oral dual antiplatelet drugs (Fig. 4C).

Another subgroup analysis included 7 studies with available data. In the short-term subgroup with 3 studies (n=564) (26,32,33), the PAgT in the experimental group was significantly reduced compared to the control group [SMD=-1.78, 95% CI (-2.46, -1.09), P<0.001]. This short-term subgroup exhibited substantial heterogeneity (I^2=90.6%, P<0.001). In the long-term subgroup with 4 studies (n=412) (30,31,34,35), the experimental group also showed a significant reduction in PAgR [SMD=-0.71, 95% CI (-0.96, -0.47), P<0.001]. In contrast, this long-term subgroup showed low heterogeneity (I^2=33.0%, P=0.215). The overall effect was significant [SMD=-1.19, 95% CI (-1.71, -0.67), P<0.001] under the random-effects model. However, heterogeneity was observed across all studies (I^2=92.4%, P<0.001). This indicates that the inhibitory effect of tirofiban on platelet aggregation was more pronounced in the short-term subgroup, while the heterogeneity in the long-term subgroup significantly decreased (Fig. 4D).

PAdR. Data were obtainable from 7 studies (26,30-35), encompassing a total of 976 patients, among whom 501 were allocated to the experimental group and 475 to the control group. A random-effects model was used owing to significant heterogeneity (I^2=83.0%, P<0.1). Overall, it was demonstrated that the experimental group had a lower PAdR compared to the control group [SMD=-1.00, 95% CI (-1.34, -0.66), P<0.01]. Subgroup analysis was carried out based on distinct intervention modalities, specifically, tirofiban in combination with oral single antiplatelet or oral dual antiplatelet drugs. In the oral single antiplatelet drug subgroup, two studies (26,31) were incorporated, comprising 193 patients in total. Of these, 101 participants were allocated to the experimental group and 92 to the control group. It was ascertained that the experimental group had a lower PAdR than the control group [SMD=-0.76, 95% CI (-1.05, -0.47), P<0.01]. In the oral dual antiplatelet drug subgroup, five studies (30,32-35) were included, involving 783 patients, with 400 in the experimental group and 383 in the control group. The results indicated that the experimental group had a lower PAdR than the control group [SMD=-1.10, 95% CI (-1.56, -0.64); P<0.01]. Evidently, for the PAdR results, the experimental group in the subgroup using tirofiban and oral dual antiplatelet drugs had a significantly more significant PAdR reduction than the control group. Furthermore, this reduction was more pronounced than the subgroup using oral single antiplatelet drugs (Fig. 5A).

Effective rate. A total of 8 studies (25,27,29,31,32,34,35,38) regarding the determination of the effective rate were comprehensively analyzed. Data were obtainable from these studies, encompassing 776 patients, among whom 388 were

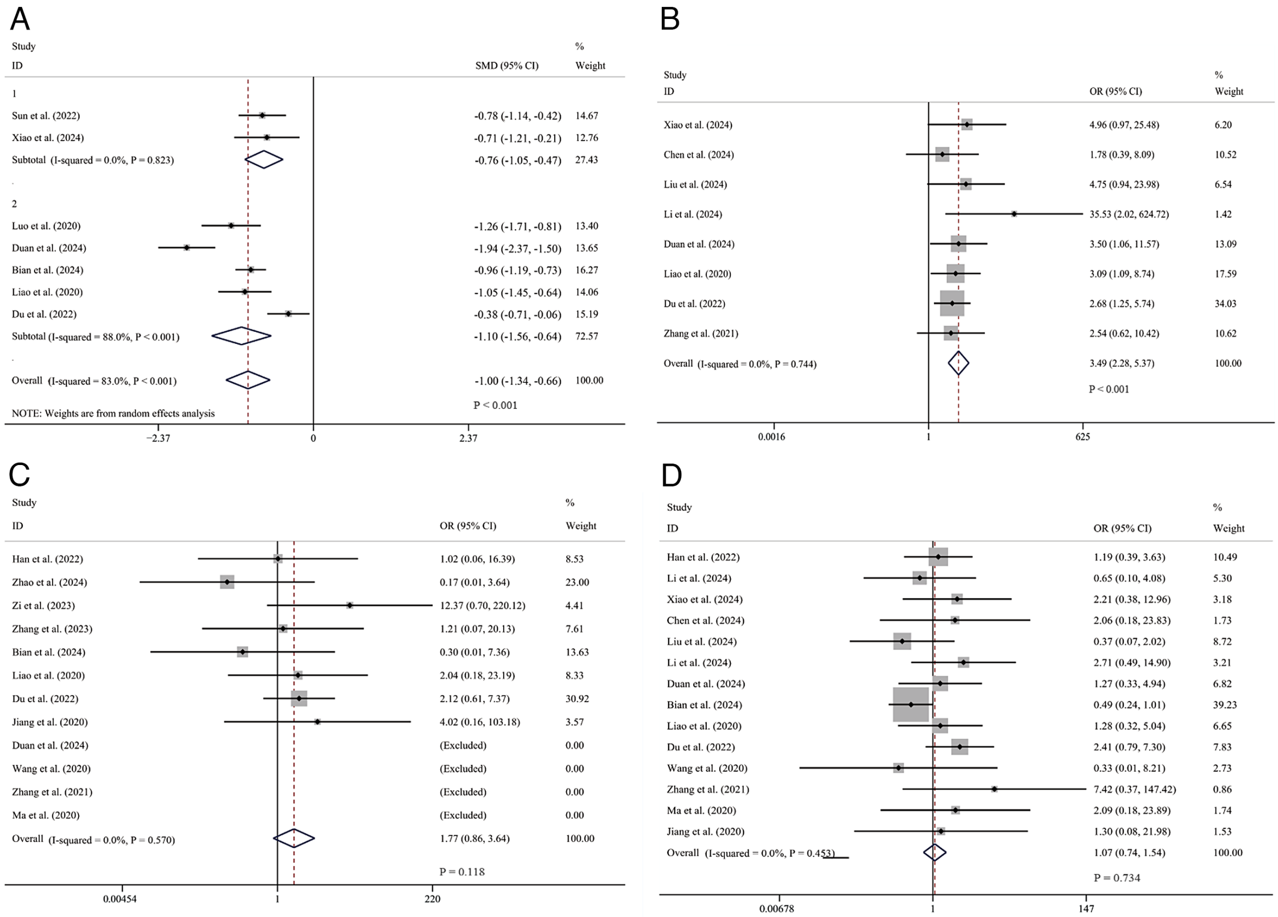

Figure 5. Forest plots comparing tirofiban therapy with non-tirofiban therapy. (A) Subgroup PAdR. (B) Effective rate. (C) sICH. (D) Other ICH. PAdR, platelet adhesion rate; sICH, symptomatic intracerebral hemorrhage; ICH, intracranial hemorrhage; 1, oral single antiplatelet drug; 2, oral dual antiplatelet drugs; SMD, standard mean deviation; CI, confidence intervals; OR, odds ratio.

in the experimental group and 388 in the control group. Heterogeneity was negligible (I^2=0.0%, P=0.744), and thus a fixed-effects model was used. Overall, it was found that the experimental group had an advantage over the control group [OR=3.49, 95% CI (2.28, 5.37), P<0.01] (Fig. 5B).

Safety outcomes

Symptomatic intracerebral hemorrhage. A total of 12 studies (10,23,24,32-40) focusing on sICH were comprehensively analyzed. Data were obtainable from these studies, including a total of 3,086 patients, with 1,574 in the experimental group and 1,512 in the control group. No significant heterogeneity was found (I^2=0.0%, P>0.1), and a fixed-effects model was used. Overall, no significant difference was found in the incidence of intracranial hemorrhage between the two groups [OR=1.77, 95% CI (0.86, 3.64), P=0.118] (Fig. 5C).

Other intracranial hemorrhage. A total of 14 studie s (23,25,27-29,31-36,38-40) concerning other intracranial hemorrhages were comprehensively analyzed. Data were obtained from these studies, comprising 1,835 patients, 920 in the experimental groups and 915 in the control groups. No significant heterogeneity was detected (I^2=0.0%, P>0.1), and a fixed-effects model was employed. Overall, no significant difference in the incidence of cerebral hemorrhage was observed between the two groups [OR=1.07, 95% CI (0.74, 1.54), P=0.734] (Fig. 5D).

Mortality rate. A total of 5 studies (23,24,36-38) regarding the mortality rate were comprehensively analyzed. Data were obtainable from these studies, which included 1,068 patients, among whom 543 were in the experimental group and 525 in the control group. Given the presence of moderate heterogeneity (I^2=45.3%), a random-effects model was used for the meta-analysis. Overall, the two groups showed no statistically significant difference in mortality rates [OR=0.40, 95% CI (0.07, 2.35), P=0.098] (Fig. 6A).

Serious adverse events. A total of 3 studies (24,35,37), involving 649 patients (335 in the experimental group and 314 in the control group), were included in the meta-analysis of serious adverse events. Under the random-effects model, the analysis showed no heterogeneity among the studies (I^2=0%, P=1.00), indicating that pooling their results was appropriate. The pooled analysis demonstrated that there was no statistically significant difference in the incidence of serious adverse events between the two groups [OR=1.10, 95% CI (0.33, 3.64), P=0.88 for effect] (Fig. 6B).

Sensitivity analyses. To assess the robustness of the results of the analyses of the present study for possible bias due to study design heterogeneity, pre-specified sensitivity analyses were

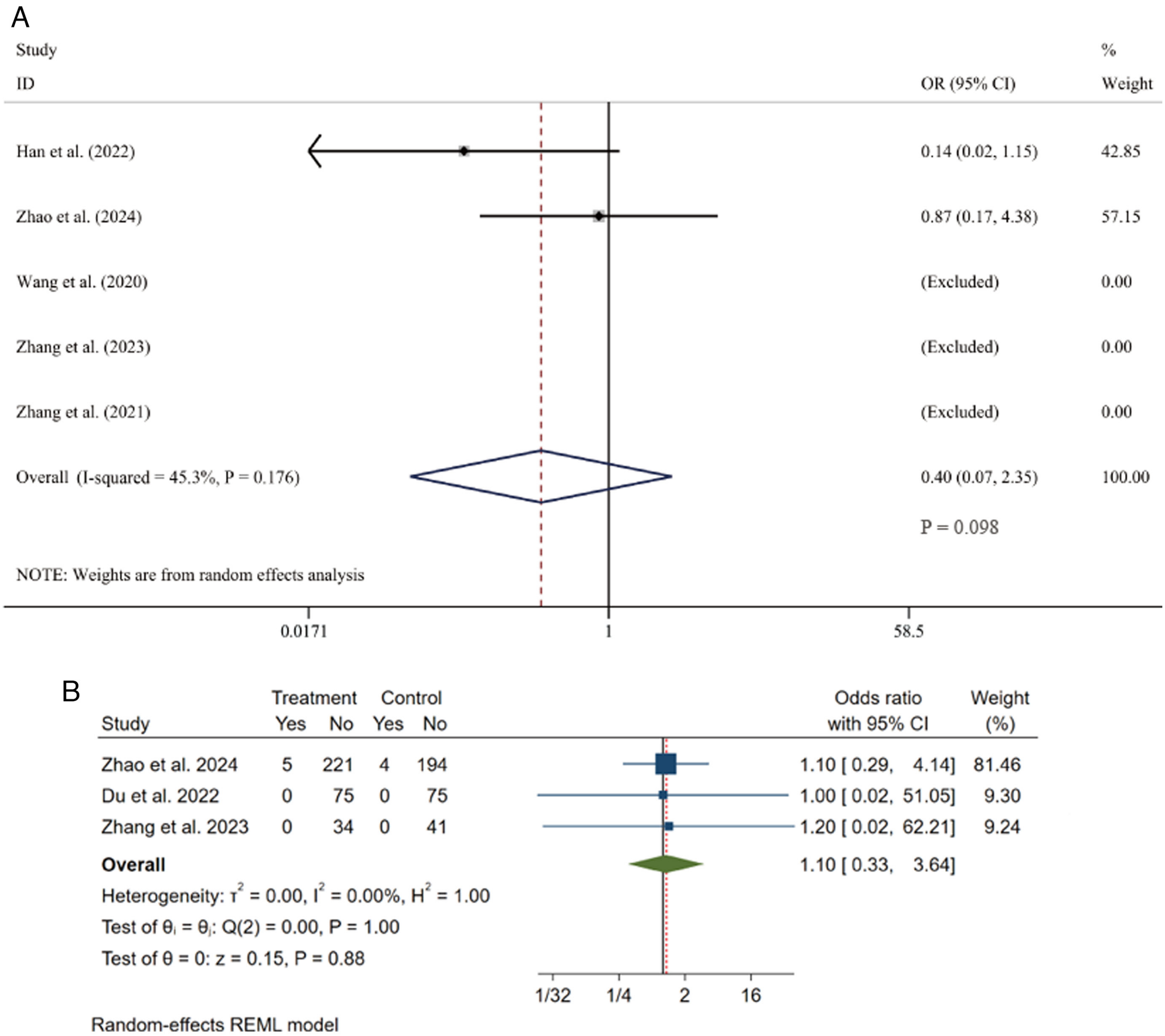

Figure 6. Forest plots for the meta-analysis of tirofiban vs. control. (A) Mortality rate. (B) Serious adverse events after treatment. CI, confidence intervals; OR, odds ratio.

performed, limited to RCTs. Functional recovery (90mRS 0-2) showed the same effect size (OR=1.31), there was a 95% CI overlap (1.10-1.58 vs. 1.06-1.59) and the I^2 increased from 0 to 2.6%. The NIHSS showed a 15% increase in effect size (SMD=-1.22 to -1.41) and the I^2 decreased from 80 to 67%. The safety profile remained stable, with no substantial change in the risk of sICH (OR=1.773 vs. 1.524) or mortality (OR=0.40). It is important to note that secondary outcomes including mRS, ADL and BI indices remained consistent in the direction of the effect, although only RCTs had wider CIs. When limited to RCT evidence, the persistence of treatment effects confirms the reliability of the primary conclusions of the present study (Table SII). The robustness of the main study results was verified. At the same time, future RCTs using standardized regimens (e.g., unified tirofiban dosing regimens) may reduce residual heterogeneity.

Publication bias. Publication bias was assessed using Egger's test and Begg's test, which showed no significant evidence of publication bias (P=0.861) (Fig. 7A), which was also confirmed by Begg's test (P=0.373) (Fig. 7B), indicating that the pooled effect size was not significantly affected by publication bias. Visual examination of the funnel plot (Fig. 7C) revealed a slight asymmetry, but in combination with statistical tests, this asymmetry is more likely to be due to random variation in a small-sample study than to systematic bias. Overall, the study was at low risk of publication bias and the reliability of the results was somewhat supported.

Impact of methodological biases on outcomes. Inadequate allocation concealment and unblinding can lead to bias in assessing treatment effects. However, there are three pieces of evidence supporting the reliability of the primary conclusion: First, the objective safety outcomes remain unaffected; they rely on imaging or laboratory confirmation, and are less susceptible to detection bias. Second, the results from different study designs are consistent: The forest plots (Fig. 3) show that the effect direction of all efficacy outcomes (e.g., NIHSS,

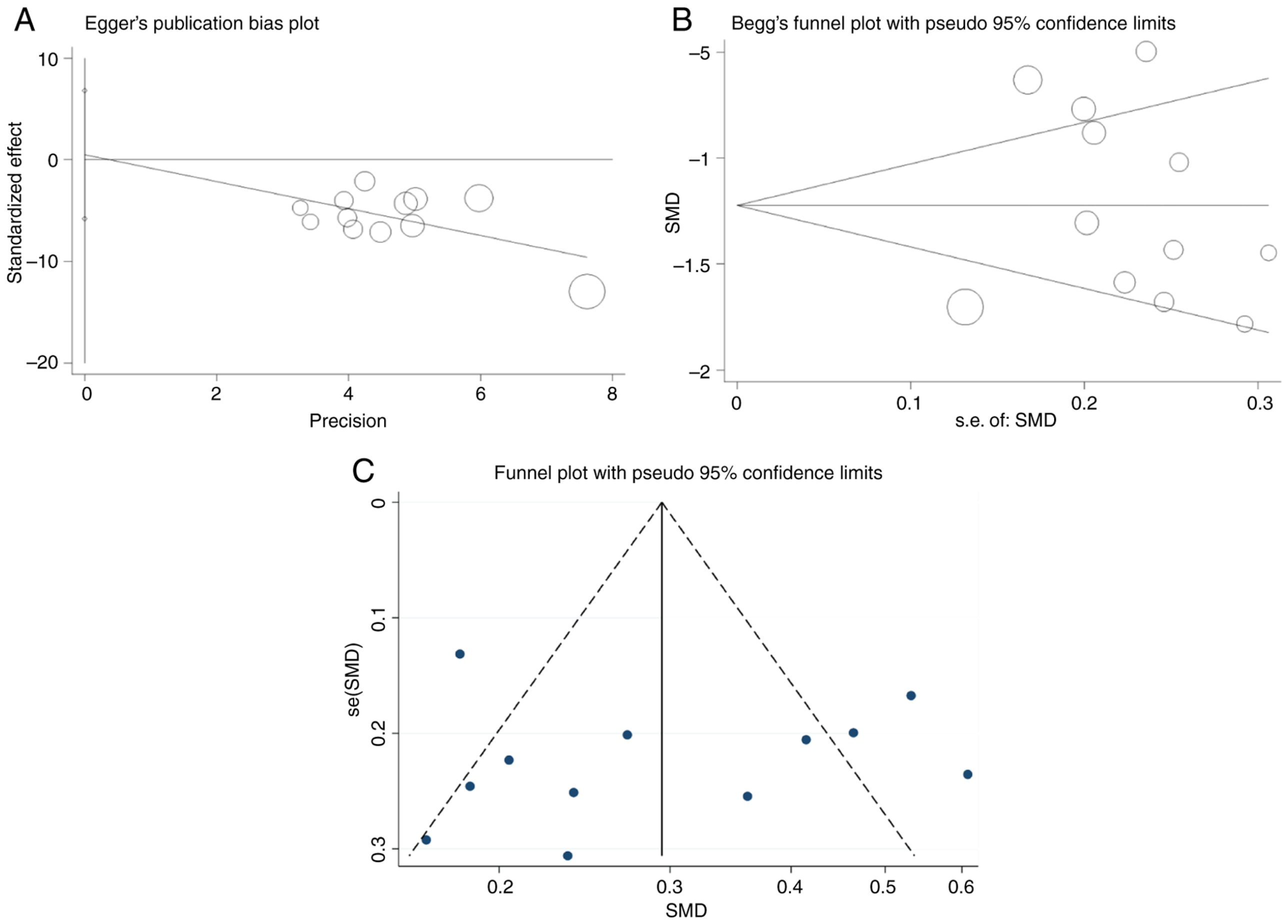

Figure 7. Publication bias. (A) Egger's regression plot; (B) Begg's regression plot; and (C) funnel plot. SMD, standardized mean difference; s.e., standard error.

mRS, ADL) is consistent in both RCTs and observational studies. Third, the sensitivity analysis confirms that excluding studies with a high risk of bias did not result in substantial changes to the effect estimates [e.g., after removing three non-blinded RCTs, the mean difference in NHISS changed from -1.22 to -1.09, as indicated by the sensitivity analysis (data not shown)]. Therefore, although the extent of functional improvement may be moderately overestimated, the treatment effect shows a positive trend, with statistical significance and safety thoroughly validated.

Discussion

The present meta-analysis aimed to confirm the safety and effectiveness of combining tirofiban with oral antiplatelet drugs for treating patients with PIS. A total of 3,667 patients from 19 articles were incorporated in the analysis. This combination can improve the patients' neurological function, as indicated by the NIHSS, ADL and mRS scores. The experimental group, receiving tirofiban injection, had a significantly better neurological improvement effect and comparable safety. In addition, this analysis also showed that tirofiban has a more substantial effect to inhibit thrombosis formation.

Prior to this, meta-analyses have indicated that tirofiban may enhance neurological functional outcomes and lower the 3-month mortality rate of patients with acute ischemic stroke treated with endovascular methods (41,42). Furthermore, tirofiban has been shown to have the effects of improving prognoses and reducing patient mortality in those undergoing mechanical thrombectomy (43) or those treated with a combination of tirofiban and intravenous thrombolysis for acute ischemic stroke (44). However, for PIS, no meta-analysis to date has evaluated the efficacy of combining tirofiban with oral antiplatelet agents. During the treatment of PIS, this combination therapy represents a promising research direction.

Atherosclerosis is an important pathological basis affecting cerebrovascular and cardiovascular diseases. Platelet activation is the key step, thus becoming an important potential target for antiplatelet therapy (45). At present, the commonly utilized antiplatelet drugs in the clinical setting encompass cyclooxygenase inhibitors represented by aspirin, P2Y12 receptor antagonists represented by clopidogrel and glycoprotein (GP)IIb/IIIa receptor antagonists represented by tirofiban, among others. Aspirin has emerged as the gold standard for antiplatelet treatment (46-48). Tirofiban is a new type of antiplatelet aggregation drug that reduces thrombosis by inhibiting the formation of fibrinogen (the bridge between adjacent platelets) (49,50). By contrast, compared to tirofiban, aspirin and clopidogrel have limited ability to affect other molecular pathways, particularly GPIIb/IIIa, as the receptor activation state is hardly influenced. As a result, they may be less effective in suppressing platelet aggregation and thrombosis formation (51). Therefore, based on the analysis results, aspirin, clopidogrel, or their combination was selected as the control group for antiplatelet aggregation treatment. The total effective rate of patients who received tirofiban injections was higher than of those who did not. Furthermore, the improvement in platelet aggregation rate and adhesion rate was also better in the injection group than in the non-injection group.

Among them, antiplatelet aggregation is key to treating progressive stroke (52). In actual clinical practice, dual anti-platelet therapy is only practical for ~70% of patients. For ~30% of patients, symptoms continue to progress even after administering loading doses. The possible reasons for this are as follows: Firstly, both aspirin and clopidogrel act on the intermediate pathways of platelet aggregation and their mechanisms of action do not fully cover all the signaling pathways that trigger platelet aggregation. Secondly, certain patients have clopidogrel resistance and the oral absorption of this drug is relatively slow, thus failing to achieve the desired effect (53,54). By contrast, tirofiban disrupts the normal function of the platelet GPIIb/IIIa receptor, which represents an effective mechanism for inhibiting thrombosis formation. Additionally, tirofiban can reduce the release of serotonin from platelets, thereby alleviating microcirculatory vasospasm from a hemodynamic perspective (55).

In addition, tirofiban may inhibit the formation of micro-thrombosis in capillaries. Experiments have shown that tirofiban also exerts additional beneficial effects by modulating cerebral microcirculation. As a GPIIb/IIIa inhibitor, it inhibits the formation of micro-thrombosis by blocking the ultimate common pathway of platelet aggregation, reducing the adhesion and aggregation of platelets at the site of microvascular injury (56,57). Experimental and clinical evidence suggests that tirofiban reduces the release of the platelet-derived vasoconstrictor serotonin (serotonin). Tirofiban, as a platelet glycoprotein class IIb receptor antagonist, relieves micro-vasospasm by inhibiting platelet glycoprotein receptors, specifically binding to fibrinogen and blocking them, preventing platelet aggregation, thereby reducing the release of serotonin (58). Furthermore, tirofiban has the characteristics of rapid onset and short half-life, with platelet function recovering in ~50% of patients within 4 h after drug discontinuation.

Although previous studies have reported an increased risk of intracranial hemorrhage with tirofiban in patients with acute ischemic stroke (14,36), the present analysis focused specifically on patients with PIS and did not find an increased risk of hemorrhage. This difference may stem from the following key differences: First, the dosing regimen used in the included studies of this meta-analysis was lower than that commonly reported in neurointerventional settings [e.g., a lower-dose regimen of 0.4 μg/kg/min for loading and 0.1 μg/kg/min for maintenance in our cohort vs. a higher loading dose of 0.4 μg/kg/min for 30 min followed by 0.1 μg/kg/min maintenance, as used in some prior stroke trials (14,36)], and it is established that higher loading doses may increase the risk of bleeding (59). The cohort did not receive any concomitant thrombolytic therapy, which is associated with an increased risk of bleeding when synergistic with GPIIb/IIIa inhibitors. Therefore, differences in patient selection and dosing regimens collectively reduce the risk of bleeding in this study cohort, resulting in inconsistent results from previous studies. The present meta-analysis clarifies that tirofiban effectively prevents platelet aggregation and thrombosis formation without elevating the risk of bleeding events, and there was no statistical difference in the safety outcomes.

Meanwhile, large RCTs, such as the CHANCE and POINT trials, have consistently indicated that combining clopidogrel with aspirin is more effective than aspirin alone in reducing the risk of early neurological deterioration (60,61). Furthermore, there is no difference in safety (62). When treating patients with acute mild to moderate stroke, dual antiplatelet therapy may be a better option than aspirin alone. In addition, this meta-analysis also conducted a subgroup analysis. The experimental group receiving tirofiban with oral dual antiplatelet drugs showed a significantly greater reduction in NIHSS score, PAgR and PAdR than those receiving tirofiban with oral single antiplatelet drugs.

However, this finding should be regarded as a hypothesis rather than conclusive evidence. Given the lack of direct comparisons of these treatment regimens in RCTs, the observed advantages may be influenced by confounding factors such as baseline severity of stroke or concomitant medication, and therefore should be interpreted with caution. Future studies should specifically assess the safety and efficacy of dual antiplatelet therapy combined with tirofiban for the treatment of PIS before clinical recommendations are made. Until dedicated RCTs confirm the benefit-risk profile, we advise against the routine clinical adoption of this approach.

For sources of heterogeneity, subgroup analyses based on the course of tirofiban revealed different patterns of heterogeneity. Both short and long courses showed significant improvement in NIHSS scores, but high heterogeneity remained highly heterogeneous, suggesting that factors other than the course of treatment (e.g., baseline severity, concomitant medications, etc.) may contribute to this variability. For PAgT, heterogeneity was significantly reduced in the long-course subgroup, suggesting that a longer course may stabilize inhibition of platelet aggregation and may be more consistent in the regulation of platelet function over time. However, the effect size of a shorter course was larger, which may reflect a more rapid antiplatelet response in the acute setting. These findings suggest that duration of treatment is a partial source of PAgT heterogeneity, but not of NIHSS heterogeneity, highlighting the complexity of prognostic factors.

Of note, the present study had certain limitations. First, incomplete data precluded subgroup analyses by stroke subtype, which may mask other sources of heterogeneity. Although the length of treatment explained the heterogeneity related to PAgR to a certain extent, there was still unexplained heterogeneity in NIHSS scores, suggesting that other influencing factors need to be further explored in future studies to supplement and improve. Second, with regard to safety outcomes, there was a lack of standardized definitions of sICH in the other included studies. While 18 trials (94.7%) used trial-specific criteria, only one study adopted the European Cooperative Acute Stroke Study III definition (24). This can lead to aggregate estimates that may underestimate the true security risk. Nonetheless, there is clinical consistency in all definitions of sICH, which include two core elements of radiographic confirmation of intracerebral hemorrhage and neurological deterioration. Studies with broader criteria may have included more borderline cases, while studies with more stringent definitions may have counted fewer events. Similarly, although the definition of mortality is relatively consistent (all-cause mortality during a given follow-up period), subtle differences in the length of follow-up between studies (e.g., 30- vs. 90-day mortality) may have affected the pooled results. These inconsistencies limit the accuracy of the present safety conclusions and highlight the need for broadly recognized standards for future studies. Third, the trials included in the present study consist of RCTs and non-RCTs. The level of evidence is relatively low. Furthermore, although updates and analyses were made to include recent RCTs, the pooled sample size was still insufficient. Heterogeneity is mainly due to differences in antiplatelet regimens and dosing strategies. However, the direction of the effect of each trial suggests the potential of tirofiban in a particular subgroup. At the same time, more large-scale, multi-center clinical trials are needed in the future. Furthermore, the generalizability of the present findings may be limited by geographical bias, as the included studies were predominantly conducted in a single region (China). In addition, although the NIHSS deterioration threshold varied (2-4 points gain), all studies met the set core criteria for deterioration of neurological function at 72 h. This agreement improves comparability, but heterogeneity related to thresholds still needs to be taken into account when interpreting the NIHSS. Finally, the included RCTs had a high risk of blinding and selection bias, or were unclear in terms of bias, which may have exaggerated estimates of functional outcomes.

Although all observational studies scored NOS ≥7 points, this reflects incidental retrieval rather than intentional selection. Should there be any studies with lower NOS scores in the future, they can be included in an updated meta-analysis to validate the generalizability of the findings of the present analysis.

In conclusion, the present meta-analysis showed that in PIS, tirofiban injection combined with aspirin and clopidogrel showed the potential to improve neurological deficits, inhibit platelet aggregation and improve clinical efficacy in patients and had a good safety profile, but it needs to be validated by further large-sample, multi-center, prospective RCTs of antiplatelet strategies before widespread clinical use.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YY conceived and designed the study, searched and screened the literature, extracted data, applied software and prepared the first draft. THD extracted data and applied software. YFJ supplemented data and revised the manuscript. YY and YFJ checked and confirmed the authenticity of the raw data. YCL and JWG selected the research topic, designed and planned the study and reviewed the manuscript. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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